Appeal No. 2017-1480

United States Court of Appeals
for the
Federal Circuit

AMGEN INC., AMGEN MANUFACTURING LIMITED, AMGEN USA, INC.,

Plaintiffs-Appellees,

– v. –

SANOFI, AVENTISUB LLC, REGENERON PHARMACEUTICALS INC., SANOFI-AVENTIS U.S., LLC,

Defendants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE IN CASE NO. 14-1317-SLR JUDGE SUE L. ROBINSON

BRIEF OF *AMICI CURIAE* PFIZER INC. AND IPSEN PHARMA S.A.S. IN SUPPORT OF DEFENDANTS-APPELLANTS AND REVERSAL OF THE DISTRICT COURT'S DECISION ON WRITTEN DESCRIPTION

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   Pfizer Inc.

2. The name of the real party in interest represented by us is:

   Pfizer Inc.

3. All parent corporations and any publicly held companies that own 10% or more of the stock of the party or *amicus curiae* represented by us are:

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Pfizer Inc. ("Pfizer") and Ipsen Pharma S.A.S. ("Ipsen") submit this brief as *amici curiae* pursuant to Rule 29 of the Federal Rules of Appellate Procedure and this Court's Rule 29. The parties to this case have consented to the filing of this brief.

I. INTEREST OF THE *AMICI CURIAE*

Pfizer is a global pharmaceutical company that discovers, develops, and markets innovative medicines, including monoclonal antibodies. Ipsen is a specialty-driven biopharmaceutical company that develops and markets new medicines, including biological drugs, for targeting debilitating diseases in various therapeutic areas. Antibodies comprise an important aspect of current clinical research in numerous therapeutic areas under investigation by *amici curiae* and other companies. Patents with functional claims that encompass a broad genus of antibodies having no identifiable common structural features threaten the development and commercialization of these products.

The asserted claims of Amgen's U.S. Patent Nos. 8,829,165 (the "'165 patent") and 8,859,741 (the "'741 patent") functionally define a genus of monoclonal antibodies based on their ability to bind to one or two amino acid residues in the sequence of the PCSK9 protein and block binding of PCSK9 to low density lipoprotein receptor ("LDLR"). The asserted claims do not define any antibody by its structure or amino acid sequence. The claims' reference to amino acids on PCSK9, a well-known antigen neither discovered nor characterized by Amgen, does nothing to cure these fatal defects. This appeal therefore provides the Court with an opportunity to clarify the application of the written description requirement to such functional claims.

Amici curiae have no direct stake in the result of this appeal. In 2016, Pfizer discontinued efforts to commercialize bococizumab, an antibody that inhibits PCSK9 and that was under investigation for the treatment of elevated cholesterol. At present, Pfizer is not developing an anti-PCSK9 antibody for regulatory approval. *Amici curiae* are hopeful that the Court will consider the arguments herein and reverse the judgment entered by the District Court and conclude that Amgen's functionally-defined antibody claims are invalid as a matter of law for failure to comply with the written description requirement under 35 U.S.C. § 112.

Pursuant to Federal Rule of Appellate Procedure 29(a)(4)(E), *amici curiae* state that no party or counsel for any party to this appeal authored this brief in whole or in part, and no person other than *amici curiae* or their counsel contributed money toward the preparation or submission of this brief.

II. INTRODUCTION

The purpose of the written description requirement is to "ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353-54 (Fed. Cir. 2010) (*en banc*) (*quoting Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920 (Fed. Cir. 2004)). This requirement is "part of the *quid pro quo* of the patent grant and ensures that the public receives a meaningful disclosure in exchange for being excluded from practicing the invention for a period of time." *Id*. at 1354.

Compliance with the written description requirement is particularly necessary when a patent applicant claims an invention based on its function (what it does) rather than its structure (what it is). This is because such claims, when allowed, often encompass a broad and diverse range of structures beyond those described in the patent. As a result, they pose significant risks to competitors and tend to discourage investment in competing products. The written description requirement ensures that patent applicants are unable to preempt future innovators by obtaining claims that are far broader than their actual invention. *See Ariad*, 598 F.3d at 1353.

This case represents a classic example of preemptive, overly broad functional claiming in violation of the written description requirement. PCSK9 was a known antigen as of the priority date of the '165 and '741 patents. Amgen did not discover PCSK9 or its amino acid sequence, did not discover that PCSK9 interacts with the LDLR, and did not discover that inhibiting this interaction lowers cholesterol levels. These discoveries were made by other scientists and were publicly known as of the priority date, including the specific region on LDLR to which PCSK9 binds. The Amgen inventors simply screened for antibodies that bound to PCSK9 and blocked the binding of PCSK9 to LDLR. Rather than claiming those specific antibodies based on their amino acid sequences, or similar structurally-defined antibodies, Amgen set out to obtain claims covering any antibody that binds PCSK9 and blocks its binding to LDLR. The asserted claims thus cover many millions of different antibodies, of unknown structure and properties. The additional limitations in the claims reciting particular amino acid residues on PCSK9 to which the antibodies must bind do not effectively define or limit that large genus.

The evidence at trial established that only two of the antibodies disclosed in the patents, 21B12 and 31H4, fell within the scope of the broadly defined genus claims. Not surprisingly, the asserted claims cover antibodies far different than those described in the patents, including Appellants' later-discovered Praluent® and Pfizer's bococizumab. Amgen thus did not possess the entire genus of antibodies at the time they filed their patent application, and certainly could not have envisioned the amino acid sequence or properties of these independently-discovered therapeutic antibodies. Yet, they obtained claims that cover those antibodies and countless others. These are precisely the types of functional claims that the written description requirement is designed to prevent.

To be clear, *amici curiae* are not arguing that patentees should not seek to retain the exclusivity provided by their patents; indeed, this "right to exclude is a fundamental tenant of patent law." *Edwards Lifesciences AG v. Corevalve, Inc.*, 699 F.3d 1305, 1314 (Fed. Cir. 2012). However, in exchange for such rights, the patentee must provide a full description of an invention in his or her *possession* such that the public receives a "meaningful disclosure" in exchange for being excluded from practicing the invention. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 970 (Fed. Cir. 2002). In this case, Amgen did not live up to its end of the bargain based on the limited disclosure of only *two* antibodies that bind to a vaguely-defined "region" on PCSK9.

Unless this Court clarifies the written description requirement as it applies to functionally-defined antibody claims, patent applicants will continue to pursue such claims and enforce them against competitors. The result will be more uncertainty and risk for innovators and, worse yet, fewer or more expensive treatment options for patients.

III. ARGUMENT

A patent applicant can satisfy the written description requirement for functional genus claims in one of two ways: by disclosing either "a representative number of species falling within the scope of the genus" or "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350. The asserted claims of the '165 and '741 patents encompass a broad range of antibodies that may bind to a number of ill-defined or undefined epitopes on PCSK9 and block binding to LDLR, yet the patent specification discloses only two antibodies known to satisfy the claims. The asserted claims are therefore invalid for lack of adequate written description.

The asserted claims of the '165 patent are claims 2, 7, 9, 15, 19, and 29. All but claim 29 depend from claim 1, which is as follows:

> An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following resides: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

Claims 2, 7, 9, and 15 recite single amino acid residues listed in claim 1, while claim 19 requires binding to at least two of the amino acids:

> 2. The isolated monoclonal antibody of claim 1, wherein the monoclonal antibody binds to at least S153.
>
> 7. The isolated monoclonal antibody of claim 1, wherein the monoclonal antibody binds to at least D238.
>
> 9. The isolated monoclonal antibody of claim 1, wherein the monoclonal antibody binds to at least I369.

> 15. The isolated monoclonal antibody of claim 1, wherein the monoclonal antibody binds to at least V380.
>
> 19. The isolated monoclonal antibody of claim 1, wherein the monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3.

Asserted claim 29 is independent and is as follows:

> A pharmaceutical composition comprising an isolated monoclonal antibody, wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3 and blocks the binding of PCSK9 to LDLR by at least 80%.

Amgen also asserted claim 7 of the ’741 patent. Claim 7 depends from claim 2, which in turn depends from claim 1. Claims 1, 2 and 7 are as follows:

> 1. An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.
>
> 2. The isolated monoclonal antibody of claim 1, wherein the isolated monoclonal antibody is a neutralizing antibody.
>
> 7. The isolated monoclonal antibody of claim 2, wherein the epitope is a functional epitope.

A. Appellees Did Not Disclose Representative Species Within the Broadly Claimed Genus

“When a patent claims a genus using functional language to define a desired result, ‘the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.'" *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1299 (Fed. Cir. 2014) (*quoting Ariad*, 598 F.3d at 1349). In other words, "one needs to show that one has truly invented the genus, *i.e*., that one has conceived and described sufficient representative species encompassing the breadth of the genus." *Id.* at 1300. "Otherwise, one has only a research plan, leaving it to others to explore the contours of the claimed genus." *Id*.

In *AbbVie*, the claims at issue were directed to a human antibody that binds to and neutralizes IL-12, as measured by k_{off} rate constants recited in the claims. The patent specification disclosed the amino acid sequence of about 300 antibodies having various binding affinities to IL-12. These antibodies were 90% or more identical to one another based on their amino acid sequences. The accused product, Stelara®, only had about 50% sequence identity (in the variable region) yet fell within the scope of the asserted claims. On appeal, this Court held that the asserted claims were invalid for lack of adequate written description of the claimed genus, explaining that "the asserted claims attempt to claim every fully human IL-12 antibody that would achieve a desired result, *i.e*., high binding affinity and neutralizing activity, and cover an antibody as different as Stelara®, whereas the patents do not describe representative examples to support the full scope of the claims." *AbbVie*, 759 F.3d at 1301.

Here, the claims are not as specific as those in *AbbVie*. Amgen's asserted claims define the antibody in purely functional terms, *i.e.*, based on its ability to bind to one or two amino acid residues when bound to PCSK9 and to block binding to LDLR. The claims are in essence a research plan for making antibodies of any type to what could be a number of different undefined epitopes. For example, claims 1, 19, and 29 of the '165 patent recite fifteen amino acids on PCSK9 that may form part of the region in the three-dimensional structure of PCSK9 that binds to LDLR. *See* '165 patent, col. 100, ll. 5-10. The evidence at trial demonstrated that this region encompasses *at least* the two epitopes that 21B12 and 31H4 bind to. *See Amgen Inc. v. Sanofi*, 14-cv-1317, D.I. 389 at 13-14 (D. Del.) ("District Court Opinion"). But the asserted claims are not limited to antibodies that bind only in this region. They also encompass antibodies that may bind to epitopes comprising residues on PCSK9 other than the fifteen residues recited in the claims. As a result, it is impossible for a skilled artisan to identify the epitopes on PCSK9 that antibodies bind to or to know how many antibodies the claims actually cover. It is clear that Amgen did not possess and did not provide a written description of the invention as claimed.[1]

The specification of the ’165 and ’741 patents discloses only two antibodies – 21B12 and 31H4 – known to satisfy the asserted claims. *See* District Court Opinion, at 13. There is no doubt that the claims cover antibody structures beyond just 21B12 and 31H4. Indeed, Appellants’ later-discovered anti-PCSK9 antibody Praluent® infringes the asserted claims, and Pfizer’s PCSK9 inhibitor (bococizumab) could be encompassed by the claims as well. The asserted claims as construed by the district court also encompass all classes and subclasses of human, humanized, chimeric, and non-human monoclonal antibodies and antibody fragments that meet the functional limitations of the claims, whereas the examples in Amgen’s patents (including 21B12 and 31H4) are all human monoclonal antibodies. *See* District Court Opinion, at 16 (“Dr. Siegel explained that the asserted claims were not limited to human antibodies, but could be mouse or camel antibodies. The structures of such non-human antibodies would be ‘much different’ than human antibodies”). The written description requirement must ensure that “when a patent claims a genus by its function or result, the specification recites sufficient materials to accomplish that function – a problem that is particularly

[1] Because the asserted claims are vague and ambiguous as to the epitopes to which the antibodies bind, the claims are also indefinite as a matter of law. *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

acute in the biological arts." *Ariad*, 598 F.3d at 1352-53. Amgen's disclosure of just two species clearly falls short of this requirement.

The antibodies covered by the asserted claims are not only large in number; they are structurally diverse as well. An antibody is a large, complex molecule consisting of hundreds of amino acids. As such, the number of unique structures possible based on modifications to the amino acid sequence is potentially enormous. *See, e.g.*, Tr. 869:1-22.[2] Even where the universe of such antibodies is limited to those that bind to PCSK9, the various classes of antibodies and the variation within the amino acid sequences of such antibodies is extremely high. Indeed, the two species that were determined to satisfy the asserted claims (21B12 and 31H4) are themselves diverse from one another both in terms of their amino acid sequences and their binding sites on PCSK9. District Court Opinion, at 14-15. Thus, there is extensive structural diversity and differences in properties across the *entire genus* of antibodies encompassed by Amgen's claims, well beyond what is reflected by the two species disclosed in the specification. District Court Opinion, at 16-17. Accordingly, Amgen has not described "representative examples to support the full scope of the claims." *AbbVie*, 759 F.3d at 1301.

[2] All references to the trial transcript are cited as "Tr." *See, Amgen Inc. v. Sanofi*, 14-cv-1317, D.I. 341-346 (D. Del.) (trial transcripts from March 8, 2016, March 9, 2016, March 10, 2016, March 11, 2016, March 14, 2016, March 16, 2016).

Amgen offered evidence at trial that at least twenty-two additional antibodies disclosed in their patents compete with 21B12 or 31H4 for the PCSK9 binding site and therefore fall within the scope of the asserted claims. District Court Opinion, at 19, 25. However, Amgen's own expert admitted that the data in the asserted patents does not allow a person of skill in the art to determine whether any of those antibodies bind to any *particular* residue on PCSK9. *See* Tr. 880:1-882:14. Thus, there is no basis to conclude from the patent specification that the twenty-two antibodies that compete with 21B12 or 31H4 for PCSK9 binding actually fall within the scope of any of the asserted claims, which are directed to antibodies that bind a single amino acid residue (or two residues in the case of claims 19 and 29 of the '165 patent and claim 7 of the '741 patent).

Even assuming Amgen's assertions are correct, it would not justify upholding Amgen's broad, functional claims. There is no indication that even these additional antibodies constitute a sufficient number of species within the genus claims at issue here, or that they are representative of all the diverse antibody structures encompassed by the claims. To the contrary, Appellants' expert testified that these antibodies are *not* representative. *See* District Court Opinion, at 17. If anything, Amgen's argument reinforces the notion that the claimed genus is extremely broad and that the variation within the genus is much greater than the limited number and types of structures disclosed in the specification. *See AbbVie*, 759 F.3d at 1300-1301 (disclosure of over one-hundred antibodies was insufficient to satisfy written description requirement because they were not "representative" of the structural variability of the genus).

B. There is No Evidence of Common Structural Features or a Correlation Between Structure and Function

A patentee can satisfy the written description requirement for functional genus claims by disclosing "structural features common to the members of the genus so that a person of ordinary skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350 (*quoting Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)). This includes establishing a reasonable "correlation" between the structure of the claimed molecule and its function. *AbbVie,* 759 F.3d at 1301.

In this case, there is no evidence of common structural features among the members of the claimed genus. The amino acid sequences of the two antibodies known to satisfy the asserted claims (21B12 and 31H4) differ from one another, particularly in the variable domain which largely determines where and how the antibodies bind to PCSK9. Indeed, the Complementarity Determining Regions ("CDRs") of 21B12 and 31H4 do not even contain the same number of amino acids. For example, CDR3 of the heavy chain has six amino acids in 21B12 and eleven amino acids in 31H4. *See, e.g.*, '165 patent, Figures 3C, 3E, and 3JJ. Similarly, CDR3 of the light chain has nine amino acids in 21B12 and only eight amino acids in 31H4. *See, e.g.*, *id.*, Figures 2C, 3E, and 3JJ. In fact, the only common structural features of 21B12 and 31H4 appear to be the components of all antibodies generally, *e.g.*, constant regions and framework regions that contribute to the antibodies' shape, but even these components vary in sequence and class of antibody. District Court Opinion, at 14-15, 22-23. To the extent Amgen relies on such "features" to satisfy the written description requirement, this is obviously insufficient. *AbbVie*, 759 F.3d at 1301.

Furthermore, 21B12 and 31H4 are not even representative of the entire range of antibodies encompassed by the claims. District Court Opinion, at 14-15. Thus, it is difficult to understand how Amgen can establish common structural features across all members of the genus where they are unable to do so for even the two species disclosed in their patent.

Amgen also cannot establish a correlation between the structures of the claimed antibodies and their function. Amgen's asserted claims merely recite single amino acid residues (or two residues) on PCSK9 to which the claimed antibodies must bind. As made clear by the experts at trial, knowledge of the binding site on an antigen does not allow a person of ordinary skill in the art to visualize the amino acid sequences of the corresponding antibodies and establish a correlation between those structures and their ability to bind to the antigen. *See, e.g.,* Tr. 549:2-16; 836:5-21; District Court Opinion, at 15, 21. To the extent

Amgen argues otherwise, there is no explanation of what the structure-function correlation might be in this case, assuming one even exists. *See, e.g.*, District Court Opinion, at 22-23. If binding to a particular amino acid residue on PCSK9 defines the function of the claimed antibodies, Amgen has not established what structural features are responsible for this function. Given that Amgen asserts that it disclosed over twenty antibodies which allegedly fall within the scope of the asserted claims, Amgen presumably should have been able to describe a structure-function correlation based on knowledge of these sequences, or pursued claims based on such a correlation, if it existed.

This Court has made clear that functional claims covering a large genus are "inherently vulnerable to invalidity challenge for lack of written description support, *especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus*." *AbbVie*, 759 F.3d at 1301 (emphasis added). This case is no exception. Appellees simply have not identified common structural features or established any structure-function correlation for the broad genus of antibodies covered by their claims. Accordingly, this Court should reverse the judgment on written description.

C. The Court Should Apply the Law Consistently for Small Molecules and Large Molecules

To date, most of the pharmaceutical patent cases to come before this Court in which broad functional claims were at issue involved "small" molecules. For example, in both *Ariad* and *University of Rochester*, this Court held functionally-defined small molecule claims invalid due to insufficient representative species. In both cases, this Court explained that the written description requirement must "ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Ariad*, 598 F.3d at 1353-54; *Univ. of Rochester*, 358 F.3d at 920. The rationale for the holdings in those cases is no less relevant where the claims at issue cover larger molecules, such as proteins or antibodies. Patentees should not be able use broad functional claims that encompass diverse species to unfairly "preempt the future before it has arrived," merely because they are claiming biologic drugs rather than small molecules. *Ariad*, 598 F.3d at 1353.

While one may argue that past difficulty in characterizing large molecules often necessitated, or at least justified, functional claiming, this is no longer the case today. As a result of technological advances, researchers can characterize and determine the three-dimensional crystal structure and amino acid sequence of large molecules, such as antibodies. Indeed, Amgen relied on such readily available techniques to determine the amino acid sequence and crystal structure of two of the antibodies (21B12 and 31H4) disclosed in their patents, one of which would become the antibody used in their commercial product (Repatha®). District Court Opinion, at 6, 13. In other patents not asserted here, *e.g.* U.S. Patent Nos. 8,030,457 and 8,168,762, Amgen claimed these antibodies based on their amino acid sequences, just as they would claim a novel small molecule based on its chemical formula. The only purpose of the asserted functional claims here is to preempt competition as broadly as possible and beyond the actual contribution of the inventors.

Amici curiae do not object to an innovator claiming what it has made, or claiming a genus based on disclosure of representative species, or claiming by a structural definition that permits some reasoned and predictable variation. However, Amgen's claims to the large, undefined genus of antibodies using broad functional language do not qualify as such, and are merely an attempt to "preempt the future." *Ariad*, 598 F.3d at 1353. If such claims are to be granted in the first place, and subsequently upheld in litigation, they must be subject to the same rigorous scrutiny that has been applied to functionally-defined small molecule claims. This is especially true where the claims cover structurally diverse molecules beyond those discovered and disclosed by the patent applicant.

D. The Specification Does Not Disclose a "Newly-Characterized Antigen" or Support Broad Antibody or Epitope Claims

The district court instructed the jury on written description, as follows:

> In the case of a claim to antibodies, the correlation between structure and function may be satisfied by the disclosure of a newly-characterized antigen by its structure, formula, chemical name, or physical properties if you find that the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies to such an antigen was conventional or routine.

Amgen Inc. v. Sanofi, 14-cv-1317, D.I. 299, at 25 (D. Del.) (jury instruction on "written description"). It is undisputed that the human PCSK9 sequence was known prior to the critical date of the asserted claims and was not "newly characterized" by Amgen. When Amgen generated antibodies to PCSK9 in mice by injecting human PCSK9 as the antigen, they were using a *known*, well-characterized antigen. *See* '165 patent, col. 73, ll. 47-53. Therefore, the jury instruction above was improper in this case.

1. Even under the jury instructions, the asserted claims are invalid for a lack of written description because the Appellees' patents do not describe a novel *antigen* or even a specific *epitope*

Even assuming it was appropriate for the district court to instruct the jury with its "newly-characterized antigen" instruction (it was not), no reasonable jury could find that the written description requirement was satisfied as a matter of law. *See Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 843 F.3d 1315, 1326 (Fed. Cir. 2016) ("To prevail on a renewed motion for JMOL following a jury trial, a party must show that the jury's findings, presumed or express, are not supported by substantial evidence or, if they were, that the legal conclusion(s) implied by the jury's verdict cannot in law be supported by those findings.") The asserted claims do not claim an antibody which binds a "newly-characterized antigen." Nor do Amgen's patents disclose such an antigen based on its "structure, formula, chemical name, or physical properties." PCSK9 itself was not novel, and Amgen did not discover, sequence, or characterize it. *See, e.g.*, Tr. 874:16-24. Amgen also did not discover the region on LDLR to which PCSK9 binds, or the effect of antagonizing such binding on lowering cholesterol. *See* Tr. 397:19-399:19. Accordingly, there was no basis to conclude that Amgen satisfied the written description requirement by disclosing a "newly-characterized antigen." *See Power Integrations*, 843 F.3d at 1326.

To the extent the jury relied on the disclosure of an "epitope" or specific amino acid residues on PCSK9 to satisfy the "newly-characterized antigen" test, this line of reasoning should fail as a matter of law. The jury instructions refer to a well-characterized *antigen*, not an individual *epitope* on an antigen. It would be far from "routine" to generate an antibody with only the amino acids of a single epitope, much less a single amino acid *residue*, as in Amgen's asserted claims.

Indeed, Amgen produced all of the antibodies disclosed in its patents using the *entire* PCSK9 antigen. *See* Tr. 259:4-14; ’165 patent, col. 73, ll. 38-53.

Furthermore, Amgen’s patents do not disclose an actual epitope. They disclose a binding region on PCSK9 comprised of amino acids at positions 153, 154, 155, 194, 238, 239, 369, 372, 374, 375, 377, 378, 379, 380, and 381 that bind to LDLR. *See* ’165 patent, col. 100, ll. 5-10. However, it was undisputed at trial that neither 21B12 nor 31H4 bind to all fifteen of these residues, and there was disagreement as to how many of the recited residues each antibody binds to. *See* District Court Opinion, at 14 (“21B12 and 31H4 ‘bind to very defined spots on the surface of PCSK9, [21B12] on one spot, sort of at the edge . . . of the [binding] region [and] 31H4 on the opposite edge.’”) (quoting Defendants-Appellants expert Dr. Michael Eck). Even if these fifteen amino acid residues represent an epitope, none of the asserted claims of the patents-in-suit require binding to all of those residues. Instead, the asserted claims only require that the antibody binds to one or two of the residues. The specification does not describe *any* antibody that binds to only one or two of the residues recited in claim 1, and it does not describe how many epitopes are present on PCSK9 which encompass one or two of these residues. A skilled artisan simply would not have been able to conclude that the inventors were in possession of the genus of antibodies potentially encompassed by such claims. The asserted claims are therefore impermissibly broad and nothing more than an attempt to "preempt the future." *Ariad*, 598 F.3d at 1353.

Finally, the asserted claims also fail to account for the complex nature of PCSK9's surface. PCSK9 is a large protein having "a complicated three-dimensional surface." Tr. at 563:4 (Defendants-Appellants expert Dr. Michael Eck). And while some epitopes may be linear, where "amino acids are arranged as they would be on a [ ] string," others are much more complicated and are "created by the way the protein folds into a unique shape." Tr. at 439:12-16 (Defendants-Appellants expert Dr. Jeffrey Ravetch). Such is the binding "region" identified by Amgen's claims, which includes residues 153, 154, 155, 194, 238, 239, 369, 372, 374, 375, 377, 378, 379, 380, and 381. *See* '165 patent, claim 1. Amgen's voluminous disclosure provides no aid to the skilled worker in identifying the antibodies that will bind to one or two of the recited residues on PCSK9 to meet the functional criteria of the claim. Put plainly, the recitation of specific PCSK9 residues masks the failure of the specification to teach any structure-function characteristics of the claimed antibodies. Amgen merely disclosed a general region of interest on PCSK9 and claimed any antibody that binds at that region.

2. The jury instructions were based on PTO Guidelines that are not binding and cannot reasonably be applied to modern antibody technology

The jury instruction was based on guidelines (and materials which followed from those guidelines) originally published by the USPTO in 2000, entitled "Revised Interim Written Description Guidelines Training Materials" (the "Guidelines") (available at: https://www.uspto.gov/web/offices/pac/writtendescription.pdf.)[3] The Guidelines included an example of a hypothetical claim to an "isolated antibody capable of binding to antigen X." Guidelines, at 59. The example states that "antigen X is novel and unobvious" and that the "production of antibodies against a well-characterized antigen was conventional" at the time of filing. Guidelines, at 59-60. Under these facts, the Guidelines conclude that "one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X." Guidelines, at 60.

The Guidelines, while an insight into PTO practices, are not the law. This Court has discussed the Guidelines in only three cases, none of which held that an *antibody* claim satisfies the written description requirement based on the disclosure

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3 The Patent Office revised the Guidelines in 2008, but their substance did not change. *See* Written Description Training Materials, 1st Revision (March 25, 2008), available at https://www.uspto.gov/sites/default/files/web/menu/written.pdf. The Guidelines are now "archived."

of an antigen. *See Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1351-53 (Fed. Cir. 2011); *Noelle v Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004); *Enzo Biochem*, 323 F.3d at 964. Moreover, these cases explicitly point out that the Guidelines are *not* binding authority. *See, e.g.*, *Enzo Biochem*, 323 F.3d at 964 (the "Guidelines . . . are not binding on this court"); *Noelle*, 355 F.3d at 1349 (noting the Guidelines are "persuasive authority," not binding authority).

Almost twenty years have passed since the PTO first adopted the Guidelines. Since then, technology has evolved such that the Guidelines may no longer be viable. While one may have argued in the past that it was necessary to claim large molecules functionally due to technical limitations in determining their structure and sequence, such concerns have diminished over time. Inventors are now able to characterize and claim newly discovered biologics, including antibodies, based on their amino acid sequences and structures just as they have been claiming novel small molecules based on their chemical structure for decades. Thus, the rationale underlying the use of functional claims based on a "newly-characterized antigen" as described in the Guidelines has diminished greatly with subsequent advances in antibody technology.

The asserted claims are an attempt to preempt all competition in the large genus of antibodies that may bind to a specific region on PCSK9, even though only two members of the genus were described by the patentee (21B12 and 31H4).

Both this Court and the Supreme Court have cautioned against claims that inhibit or "preempt" future innovation because they are closely tied to laws of nature or natural phenomenon. For example, in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2011), the Supreme Court held that claims directed to a method of determining metabolite levels in a patient were patent ineligible under 35 U.S.C. § 101 because they involve "well-understood, routine, conventional activity previously engaged in by researchers in the field" and "would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." *Mayo*, 566 U.S. at 73. Amgen's asserted claims are similarly based on "conventional" activity of making and screening antibodies to the naturally occurring PCSK9 protein. Amgen's alleged discovery of the specific amino acids on PCSK9 that interact with two antibodies that inhibit LDLR binding should not justify claims to functionally-defined antibodies that bind to those amino acids.

3. The jury verdict in this case may have wide reaching, negative implications

The impact of the jury verdict in this case may be sweeping. Following the verdict, commentators suggested seeking "epitope claims" to expand the scope of protection available to antibodies. For example, one commentator suggested the following:

> When drafting an antibody patent application, a question often arises of whether to include claims that define the antibody by its epitope or competitive binding properties, in addition to claiming the antibody by its amino acid sequence. The answer, as with most questions in patent law, is that it depends. It depends, mainly, on the amount of data available at the time of filing, or the likelihood that sufficient data will be generated later that could support an epitope claim… While it is still an open question of how well a claim to any antibody defined by its epitope or competitive binding properties will stand up to challenge, a claim supported by extensive testing might significantly improve the chances of validity and, at the same time, sizably expand the scope of protection around important commercial products. . . .
>
> Patent practitioners should work with their inventors to obtain as much data as possible on epitopes and competitive binding for their newly-developed antibodies, along with data showing any other functional aspects of the constructs, and consider carefully whether to include that data in the application. If presented properly, the data may support broader protection for a commercial product.[4]

This Court should not uphold the validity of overly broad, functional antibody claims based on undefined epitopes. The district court's judgment should be reversed.

IV. CONCLUSION

Amici curiae request the Court hold that Appellees have not satisfied the written description requirement with respect to the asserted claims of U.S. Patent

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[4] J. Jacobstein, *et al.*, *Blocking the Road: Antibodies and Epitope Claims*, available at: http://www.finnegan.com/resources/articles/articlesdetail.aspx?news=bc389142-8c60-4225-b960-e5b9f99605a3.

Nos. 8,829,165 and 8,859,741 and to reverse the lower court's denial of Appellants' motion for judgment as a matter of law on written description.

Dated: February 24, 2017

Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Natasha S. Johnson, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by Counsel for *Amici Curiae* Pfizer Inc. And Ipsen Pharma S.A.S. to print this document. I am an employee of Counsel Press.

On February 24, 2017, Counsel for *Amici Curiae* Pfizer Inc. And Ipsen Pharma S.A.S. authorized me to electronically file the foregoing Brief with the Clerk of Court using the CM/ECF System, which will send notice of such filing to all registered CM/ECF users.

Upon acceptance by the Court of the e-filed document, six paper copies will be filed with the Court, via Federal Express, within the time provided in the Court's rules.

/s/ Natasha S. Johnson
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CERTIFICATE OF COMPLIANCE WITH RULE 32(g)

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(a) and Federal Rule of Appellate Procedure 29(a)(5) because:

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Dated: February 24, 2017

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